(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 January 2004 (08.01.2004)

PCT

(10) International Publication Number
WO 2004/002475 A1

(51) International Patent Classification[7]: A61K 31/404, 9/20

(21) International Application Number: PCT/PL2002/000056

(22) International Filing Date: 24 July 2002 (24.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P.354823 1 July 2002 (01.07.2002) PL

(71) Applicant *(for all designated States except US)*: **PLIVA KRAKÓW, ZAKLADY FARMACEUTYCZNE S.A.** [PL/PL]; ul. Mogilska 80, PL-31-456 Kraków (PL).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **JURECZEK, Katarzyna** [PL/PL]; ul. Lasówka 44/13, PL-30-718 Kraków (PL).

(74) Agent: **DOSKOCZYNSKA-GROYECKA, Anna**; ul. Zaleskiego 9/3, PL-31-525 Kraków (PL).

(81) Designated States *(national)*: BA, EE, HR, HU, LT, LV, MK, RU, SI, UA, US.

(84) Designated States *(regional)*: European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i)) for the following designations BA, EE, HR, HU, LT, LV, MK, RU, SI, UA, European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR)*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/002475 A1

(54) Title: SUSTAINED RELEASE TABLET CONTAINING INDAPAMIDE

(57) Abstract: The present invention relates to a sustained release tablet containing indapamide and the process of manufacturing sustained release tablet containing indapamide. The tablet contains indapamide in the amount of 1.5 to 2.5% of the total mass of the tablet, lactose monohydrate in the amount of 30 to 80% of the total mass of the tablet, copovidone in the amount of 2 to 10% of the total mass of the tablet, hypromellose in the amount of 20 to 65% of the total mass of the tablet and lubricants in the amount of 0.1 to 5% of the total mass of the tablet. The process of manufacturing the sustained release tablet consists in mixing of indapamide with lactose monohydrate and copovidone and then, the mixture is moistened by purified water and the granulation process of it is performed. Next the granulate is dried, cooled, mixed with hypromellose and lubricants and compressed in tableting machine. (4 claims)

Sustained release tablet containing indapamide

The present invention relates to a sustained release tablet containing indapamide and the process of manufacturing sustained release tablet containing indapamide, known medicinal product of diuretic activity administered in the therapy of primary hypertension.

From a specification of the patent No: EP 519820 it is known a sustained release matrix tablet of indapamide and a process of its manufacturing. Sustained release is controlled by the use of methylhydroxypropylcellulose and polyvidone, the percentages of which are from 30 to 50% and from 2 to 10%, respectively, of the total mass of the tablet. The percentages of the cellulose and polyvidone compounds permit the sustained release of indapamide in a manner that is linear for a period of at least eight hours and the release of 50% of the total quantity of indapamide within a period of from 5 to 14 hours. Additionally, the percentages of cellulose and polyvidone compounds permit the sustained release of indapamide to give blood levels in humans of from 20 to 80 ng/ml at most after administration of the tablet by the oral route. A process for the preparation of an indapamide matrix tablet known from the patent No. EP 519820 is based on that there are used both a moist granulation technique and a direct compression technique, comprising the steps as follows. First, indapamide, polyvidone and lactose are mixed, then moistened with an aqueous-alcoholic solution to yield a moist mass which is then granulated, dried and then graded so as to obtain a granulate whose physical characteristics allow good filling of the moulds of a rapid compression machine. The obtained granulate is mixed with methylhydoxypropylcellulose and lubricated with magnesium stearate and

colloidal silica. The final step is compression of the lubricated mixture in a rotary compression machine, so as to obtain tablets having a hardness of approximately from 60 do 75 N.

According to the invention, the tablet for the sustained release containing indapamide contains indapamide in the amount 1.5 to 2.5% of the total mass of the tablet, lactose monohydrate in the amount of 30 to 80% of the total mass of the tablet, copovidone in the amount of 2 to 10% of the total mass of the tablet, hypromellose in the amount of 20 to 65% of the total mass of the tablet and lubricants in the amount of 0.1 to 5% of the total mass of the tablet. The aim of the use of copovidone is to bind all tablet components. Hypromellose modifies the release of the active ingredient, which is indapamide.

Magnesium stearate or/and anhydrous colloidal silica are used as the lubricants.

Hypromellose viscosity is between 1.000 to 20.000 cP.

According to the invention the process of manufacturing the sustained release tablet containing indapamide consists in mixing indapamide with lactose monohydrate and copovidone. Then, the mixture is moistened by purified water and granulated. The obtained granulate is then dried, cooled, mixed with hypromellose and lubricants and compressed in tableting machine.

The aim of the invention was to simplify the process of manufacturing the sustained release tablet containing indapamide. Additionally, it allowed replacing alcohol with water what improved safety of the manufacturing process and reduced its impact on the environment.

Examples of the invention are presented below:

Example I.

25 g of indapamide and 225 g of lactose monohydrate is mixed manually, the mixture is poured into a granulate-mixer together with 487 g of lactose monohydrate and is mixed within 1 minute with the main agitator speed 200 rpm.

Then 487 g of lactose monohydrate and 60 g of copovidone is added and all components are mixed for 1 minute with the main agitator speed 200 rpm and then with the main agitator speed 200 rpm and the side agitator speed 400 rpm.

To the prepared mixture 100 g of purified water is added within 1 minute with the main agitator speed 200 rpm and the side agitator speed 400 rpm. Then, the granulation process is performed within 4 minutes with the main agitator speed 400 rpm and side agitator speed 800 rpm.

Wet granulate is rubbed through the screen of 2.5 mm mesh and dried in the fluidal drier in the temperature 40°C to humidity content below 1 %. The dried granulate is sieved through the screen 1.2 mm mesh.

In the following step mixing of the granulate with the rest of components is performed in the rotary mixer with speed 20 rpm.

Into rotary mixer 642 g of granulate with 350 g of hypromellose is poured and mixed within 10 minutes, after which 642 g of granulate is added and is mixed within 10 minutes. Then, 350 g of hypromellose is added with 6 g of colloidal silica and is mixed within 15 minutes, after which 10 g of magnesium stearate is added and mixed within 5 minutes.

Finally tableting process of the prepared mixture is performed.

Example II.

25 g of indapamide and 225 g of lactose monohydrate is mixed

manually and next the mixture is poured into granulate-mixer together with 507 g of lactose monohydrate and is mixed within 1 minute with the main agitator speed 200 rpm.

Then 507 g of lactose monohydrate and 60 g of copovidone is added and all components are mixed within 1 minute with the main agitator speed 200 rpm and 1 minute with the main agitator speed 200 rpm and the side agitator speed 400 rpm.

To the mixture obtained in such way 100 g of purified water is dosed within 1 minute with the main agitator speed 200 rpm and the side agitator speed 400 rpm.

Next the granulation process is performed within 4 minutes with the main agitator speed 400 rpm and the side agitator speed 800 rpm.

Wet granulate is rubbed through a screen 2.5 mm mesh and is dried in the fluidal drier in the temperature 40°C to humidity content below 1 %. The dried granulate is sieved through the screen 1.2 mm mesh.

In the following step the mixing granulate with the rest of components is performed in the rotary mixer with the speed 20 rpm. Into rotary mixer 662 g of granulate with 330 g of hypromellose is poured and mixed within 10 minutes. Then, 662 g of the granulate is added and mixed within 10 minutes, after which 330 g of hypromellose together with 6 g of colloidal silica is added and mixed within 15 minutes, and next 10 g of magnesium stearate is added and mixed within 5 minutes.

Finally tableting process of the prepared mixture is performed.

The invention may be used in the industrial process of manufacturing sustained release tablets containing indapamide.

Claims

1. Sustained release tablet containing indapamide, characterized in that the tablet contains indapamide in the amount 1.5 to 2.5 % of the total mass of the tablet, lactose monohydrate in the amount 30 to 80 % of the total mass of the tablet, copovidon in the amount of 2 to 10 % of the total mass of the tablet, hypromellose in the amount of 20 to 65 % of the total mass of the tablet and lubricants in the amount of 0.1 to 5 % of the total mass of the tablet.
2. Tablet according to claim 1, characterized in that as the lubricants it contains magnesium stearate or/and anhydrous colloidal silica.
3. Tablet according to claim 1, characterized in that hypromellose viscosity is from 1.000 to 20.000 cP.
4. Process of manufacturing sustained release tablet containing indapamide, characterized in that indapamide is mixed with lactose monohydrate and copovidone and then the mixture is moisturised by purified water and its granulation is performed after which the granulate is dried, cooled, mixed with hypromellose and lubricants and compressed in tableting machine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/PL [redacted]0056

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/404 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, PASCAL, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 519 820 A (ADIR) 23 December 1992 (1992-12-23) cited in the application examples 1-5	1-4
X	DAMIEN, GERARD ET AL: "Galenic development and pharmacokinetic profile of indapamide sustained release 1.5 mg" CLINICAL PHARMACOKINETICS (1999), 37(SUPPL. 1), 13-19 , XP009004369 page 14 -page 15; table 1	1-4
A	GB 2 123 293 A (ADIR) 1 February 1984 (1984-02-01) examples	1-4

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 January 2003	31/01/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Zimmer, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/PL [redacted]0056

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 36 02 304 A (SANDOZ AG) 7 August 1986 (1986-08-07) example 11 ---	1-4
A	EP 1 057 479 A (BIOGLAN IRELAND R & D LTD ;ENBALT TRADING LTD (IE)) 6 December 2000 (2000-12-06) example 9 -----	1-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/PL [redacted]0056

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1057479 A		EP 1057479 A1	06-12-2000
		AT 199495 T	15-03-2001
		AU 4353996 A	03-07-1996
		DE 69520292 D1	12-04-2001
		DE 69520292 T2	13-06-2001
		DK 800384 T3	17-04-2001
		EP 0800384 A1	15-10-1997
		ES 2154744 T3	16-04-2001
		GB 2295966 A ,B	19-06-1996
		GR 3035863 T3	31-08-2001
		IE 950946 A1	26-06-1996
		WO 9618386 A1	20-06-1996
		PT 800384 T	29-06-2001
		ZA 9510650 A	09-07-1996